Remarks

In accordance with the present invention, there are provided methods for testing a compound for its ability to regulate transcription-activating effects of a peroxisome proliferator activated receptor-gamma (PPAR-γ). Invention methods comprise assaying for changes in the level of reporter protein present as a result of contacting cells containing PPAR-γ (either endogenous to the host cell or introduced recombinantly) and a reporter vector with the compound of interest. Compounds identified employing invention methods are useful in the treatment of pathological conditions such as diabetes.

Claims 16-20 and 27-45 were pending before this communication. By this communication, claims 16, 18-20, 27, 28 and 43-45 have been amended to define Applicants' invention with greater particularity. These amendments add no new matter and are fully supported by the specification and the original claims. Claim 17 has been cancelled without prejudice.

Accordingly, claims 16, 18-20 and 27-45 are currently pending. The present status of all claims in the application, and current amendments thereto, are provided in the listing of claims presented herein beginning on page 2.

Applicants respectfully traverse the withdrawal of claims 29-35 from consideration as allegedly being directed to a non-elected invention. The present invention, as defined by original claim 16, is directed to methods of testing a compound for its ability to regulate a PPAR-γ, by contacting cells containing a PPAR-γ and a reporter construct with a test compound. This PPAR-γ may be native (endogenously present) in the chosen cells, or introduced recombinantly into the chosen cells by a receptor expression vector. Claims 29-35 are directed to methods employing a native PPAR-γ.

Furthermore, Applicants respectfully disagree with the Examiner's assertion that "the previously examined methods requir[e] a chimeric PPAR-γ/GAL4 construct" (see Office Action, Paper No. 31, at page 2, lines 15-17). Applicants have previously noted that the PPAR-γ

contemplated for use in the methods of the present invention may be an intact receptor (such as, for example, a recombinantly introduced PPAR-γ or a native PPAR-γ) or a chimeric receptor (see specification, for example, at page 15, lines 12-16). Accordingly, Applicants respectfully submit that the withdrawal of claims 29-35 is inappropriate, and further submit that these claims are properly examined together in the present application because they are indeed drawn to the elected invention, encompassing methods employing a native PPAR-γ.

The rejection of claims 16, 27 and 28 under 35 U.S.C. § 102(b), as allegedly being anticipated by Marcus *et al., Proc. Natl. Acad. Sci.* 90:5723-5727, 1993 (hereinafter referred to as "Marcus"), is respectfully traversed. Claim 16 distinguishes over Marcus by requiring a method of testing a compound for its ability to regulate PPAR-γ. In contrast, Marcus merely utilizes known activators of PPAR to study the differential mechanisms of activation of various PPARs.

However, in order to advance prosecution and reduce the issues, and in view of the fact that claim 17 has been indicated to contain allowable subject matter, Applicants have incorporated the requirements of claim 17 into claim 16 to further define the specific hormone response element contemplated for use in the reporter vector; and claims 18 and 19 have been amended to depend from claim 16 rather than cancelled claim 17. In addition, claim 20 has been amended as an independent claim to remove the prior dependency to claim 16. Thus, claims 16 and 18-20 are now in condition for allowance.

With respect to claims 27 and 28, these claims are also clearly distinguishable over Marcus by requiring contacting the test cells with at least two compounds. Claim 27 requires contacting the cells with a test compound and at least one additional compound that is a PPAR-γ agonist. Claim 28 requires contacting the cells with a test compound and at least one additional compound that is a PPAR-γ antagonist. In contrast, Marcus does not teach or suggest the use of a second compound to determine the activity of the test compound.

Accordingly Applicants respectfully request reconsideration and withdrawal of this rejection of claims 16, 27 and 28 under 35 U.S.C. § 102(b). Applicants further submit that Marcus is also not applicable to claims 29-35 because these claims require the presence of a native PPAR-γ, which is not taught by Marcus.

The rejection of claims 36, 37 and 39-42 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Webster *et al.*, *Cell* **54**:199-207, 1988 (hereinafter referred to as "Webster") in view of U.S. Patent 6,200,802 to Greene *et al.* (hereinafter referred to as "Greene"), is respectfully traversed. Claim 36 is directed to a method of testing a compound for its ability to regulate PPAR-γ. Contrary to the Examiner's assertion that Webster "teaches a method of testing a compound for its ability to regulate transcription-activating effects of ...receptors" (see Office Action, Paper No. 31, at page 5, lines 13-14), Webster merely uses known receptor activators in a mechanistic study to localize the activation domains of the human estrogen or glucocorticoid receptors. Webster clearly does not teach or suggest the use of GAL4-PPAR-γ chimeras to test compounds for PPAR-γ regulation.

Moreover, Greene is unable to cure the deficiencies of the primary reference Webster, because it also does not teach or suggest the use of GAL4-PPAR-γ chimeras to test compounds for PPAR-γ regulation. Greene merely discloses the identification of PPAR-γ receptors.

One of skill in the art would not have had any motivation to combine these two references to arrive at the present invention methods of testing compounds for their ability to regulate PPAR-γ; and even if combined, these references would not produce the claimed invention. Both references are completely silent regarding the identification of PPAR-γ modulators using a bioassay as defined by claim 36. Moreover, the study of receptor activation in the presence of a known receptor ligand (Webster) is clearly not equivalent to the use of receptor activation for the identification of novel PPAR-γ modulators. Webster specifically uses known activators to study receptor activation because the goal of Webster is to localize functional activation domains. The presence of an unknown or test compound would be completely antithetical to the desired goal because a change in activation could no longer be

attributed solely to the receptor domains being studied to localize the activation domain. Furthermore, Greene does not even mention the use of any bioassay as claimed herein.

In contrast, the present invention focuses on identifying novel PPAR-γ modulators, rather than identifying or characterizing the receptor itself. Only Applicants have used chimeric GAL4-PPAR-γ receptors in the identification of novel compounds capable of regulating PPAR-γ from a pool of uncharacterized test compounds in an assay format amenable to high-throughput screening.

Therefore, the invention as defined by claims 36 (and claims 37 and 39-42 dependent thereon) cannot be obvious over the combination of Webster and Greene. Accordingly, Applicants respectfully respect reconsideration and withdrawal of this rejection of claims 36, 37 and 39-42 under 35 U.S.C. § 103(a).

Applicants respectfully submit that claims 43-45, as amended, are also in condition for allowance. These claims were objected to as being dependent upon a rejected base claim, claim 36. Claims 43-45 have thus been rewritten as independent claims, removing the prior dependency on claim 36.

Conclusion

In view of the above remarks, prompt and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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